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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/567,362	02/06/2006	Bernard Pierre Roques	ROQUES1	9861

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BROWDY AND NEIMARK, P.L.L.C.
624 NINTH STREET, NW
SUITE 300
WASHINGTON, DC 20001-5303

EXAMINER	
YOUNG, SHAWQUIA	

ART UNIT	PAPER NUMBER
1626	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/567,362	ROQUES ET AL.	
	Examiner	Art Unit	
	Shawquia Young	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1-6 and8* is/are allowed.

6)☒ Claim(s) *7 and 9-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-20 are currently pending in the instant application.

I. *Response to Arguments*

Applicant's arguments, filed November 13, 2007 with respect to the rejection of claims 9-12 under 35 USC 101 for non-statutory subject matter and the rejection of claim 9 under 35 USC 112, first paragraph as failing to comply with the enablement requirement have been fully considered and are partially persuasive. The rejection of claims 9-12 under 35 USC 101 has been withdrawn.

Applicants traverse the rejection of claim 9 under 35 USC 112, first paragraph as failing to comply with the enablement requirement. Applicants argue that in tables 1 and 2 on page 59 of the application demonstrate that a variety of the compounds prepared were effective in inhibiting aminopeptidase A. However, the Examiner wants to point out that Applicants' specification provides enablement for a method of inhibiting aminopeptidase in a cell (in vitro) not in a patient. Therefore, the rejection is maintained.

II. *Rejection(s)*

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 7 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As stated in the MPEP 2164.01 (a), "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue".

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have need described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

In the instant case,

The nature of the invention

The nature of the invention is drawn to a compound of formula (1), according to

any one of claims 1 to 6, characterized in that it is for use in therapeutics.

The state of the prior art and the predictability or lack thereof in the art

The state of the prior art is that the pharmacological art involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat which specific disease by what mechanism). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

The instant claimed invention is highly unpredictable as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F. 2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is the more specific enablement is necessary in order to satisfy the statute Applicants' claims are drawn to a compound according to any one of claims 1 to 6, characterized in that it is for use in therapeutics.

Applicants' claim 7 is a broad claim that encompasses the use of the instantly claimed compounds in therapeutics for the treatment of numerous diseases or disorders. Applicants have failed to state what diseases applicants considered treatable by the claimed compounds in claim 7. It is the state of the prior art that the term "therapeutics" is defined as a medical treatment of disease.

The amount of direction present and the presence or absence of working examples

The only direction or guidance present in the instant specification is minimal. There are no working examples present for the treatment of the diseases encompassed by the broad claim 7.

Test assays and procedure are provided in the specification at pages 57-60 for Inhibition assay of APA activity. Receptor activity is generally unpredictable and the data provided is insufficient for one of ordinary skill in the art in order to extrapolate to the other compounds of the claims. It is inconceivable as to how the claimed compounds can treat the extremely difficult diseases embraced by the instant claims.

Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved." See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

The breadth of the claims

The breadth of the claims is drawn to a compound of formula (1), according to any one of claims 1 to 6, characterized in that it is for use in therapeutics.

The quantity of experimentation needed

The quantity of experimentation needed is undue experimentation. One of skill in

the art would need to determine what diseases out of all conditions would be benefited by the activity of the claimed compounds and would furthermore then have to determine which of the claimed compounds in the instant invention would provide treatment of the diseases.

The level of the skill in the art

The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by *in vitro* or *in vivo* screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

The specification fails to provide sufficient support of the broad use of the claimed compounds of the invention to be used in therapeutics. As a result necessitating one of skill to perform an exhaustive search for which diseases can be treated by what compounds of the invention in order to practice the claimed invention.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which diseases can be treated by the

compound encompassed in the instant claims, with no assurance of success.

This rejection can be overcome, for example, by deleting claim 7.

Claims 10-12 and 15-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As stated in the MPEP 2164.01 (a), "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue".

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have need described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and

8. the level of the skill in the art.

In the instant case,

The nature of the invention

The nature of the invention is a method of treating arterial hypertension and directly and indirectly related diseases, which comprises administering to a patient in need thereof an efficient amount of a compound of formula 1 according to claim 1; a method for treating a disease selected from the group consisting of primary or secondary arterial hypertension, an ictus, myocardial ischemia, cardiac insufficiency and renal insufficiency, myocardial infarction, a peripheral vascular disease, diabetic proteinuria, syndrome X, glaucoma, neurodegenerative diseases and memory disorders, which comprises administering to a patient in need thereof an efficient amount of a compound of formula (1) according to claim 1; or a method of treating ischemic and tumoral pathologies in which aminopeptidase A is involved, which comprises adminstering to a patient in need thereof an efficient amount of a compound of formula (1) according to claim 1.

The state of the prior art and the predictability or lack thereof in the art

The state of the prior art is that the pharmacological art involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat which specific disease by what mechanism). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in

the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

The instant claimed invention is highly unpredictable as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F. 2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art would recognize that in regards to therapeutic effects of cognitive disorders by inhibiting aminopeptidase A would make a difference.

For example, applicants' claims are drawn to a method for treating a neurodegenerative disease. The genus term "neurodegenerative disease" embraces numerous diseases such as Alzheimer's disease, Parkinson's disease, Multiple sclerosis, etc.

Applicants' claims are drawn to the treatment of Alzheimer's disease. It is the state of the art that there is no known cure or prevention for Alzheimer's disease and that there are only four medications available in the United States available to temporarily slow the early stages of Alzheimer's disease. The current drugs for the treatment of Alzheimer disease, Aricept, Exelon, Reminyl and Cognex, treat early stages of Alzheimer's disease by delaying the breakdown of acetylcholine. Memantine, which blocks excess amounts of glutamate treats late stage Alzheimer's disease.

(URL:http://www.cnn.com/2003/HEALTH/conditions/09/24/alzheimers.drug.ap/index.html.)

In addition, Layzer, Cecil Textbook of Medicine (article enclosed), states that "some degenerative diseases are difficult to classify because they involve multiple anatomic locations" (see page 2050). Alzheimer's disease has traditionally been very difficult or impossible to prevent or even to treat effectively with chemotherapeutic agents (*See* e.g., the Cecil Textbood of Medicine, 20th edition (1996), Vol. 2, page 1994).

Applicants' claims are also drawn to a method of treating an ictus. The genus term "ictus" embraces diseases or disorders such as stroke, seizures, etc. Therefore the claims are drawn to a method of treating a stroke. Stroke represents one of the most intractable medical challenges. Stroke is estimated to cause about 15% of deaths. Even those who survive normally suffer from persistent damage, including motor and speech disturbances and/or convulsions. Despite a tremendous effort to resolve these problems, cerebrovascular therapy as so far been limited to trying to prevent further damage in areas on the margins of the ischemic focus, this trying to maintain adequate perfusion in remaining intact areas, and thereby limit progressive infarction. This is generally done surgically. Standard pharmaceutical treatment, such as antiarrhythmics and antithrombotics don't get at the cause of the stroke or the damage caused, but are mostly done to insure adequate cardiac functioning.

Applicants' claims are drawn to a method for treating tumoral pathologies. The genus term "tumoral pathologies" embraces both cancerous and non-cancerous pathologies. Therefore Applicants' claims are also drawn to a method for treating cancer. The state of the prior art is that cancer therapy remains highly unpredictable. The various types of cancers have different causative agents, involve different cellular mechanisms, and consequently, differ in treatment protocol. Cancer is a disease characterized by a population of cells that grow and divide without respect to normal limits, invade and destroy adjacent tissues, and may spread to distant anatomic sites through a process called metastasis (URL:http://en.wikipedia.org/wiki/ Cancer>). Most cancers are named for where they start. For example, lung cancer starts in the lung, and breast cancer starts in the breast. Symptoms and treatment depend on the cancer type and how advanced it is (URL: <http://www.nlm.nih.gov/medlineplus/cancer.html>>). It is known that the challenge of cancer treatment has been to target specific therapies to pathogenetically distinct tumor types, that cancer classification has been based primarily on morphological appearance of the tumor and that tumors with similar histopathological appearance can follow significantly different clinical courses and show different responses to therapy (Golub et al. page 531). Treatment may include surgery, radiation, chemotherapy, immunotherapy, monoclonal antibody therapy, etc. Furthermore, it is known that chemotherapy is most effective against tumors with rapidly dividing cells and that cells of solid tumors divide relatively slowly and chemotherapy is often less effective against them. It is also known in the prior art (Lala et al. page 91) that the role of NO in tumor biology remains incompletely understood with both the

promotion and inhibition of NO mentioned for the treatment of tumor progression and only certain human cancers may be treated by selected NO-blocking drugs. These example shows that there are different cellular mechanisms, the unpredictability in the art and the different treatment protocols. Because "cancer" refers to a class of diseases, it is unlikely that there will ever be a single "cure or treatment for cancer".

Hence, in the absence of a showing of correlation between all the diseases encompassed by the claims as capable of treatment by inhibiting aminopeptidase A, such as Alzheimer's disease one of skill in the art is unable to fully predict possible results from the administration of the compound of the claims due to the unpredictability of the inhibition of aminopeptidase A, for example, since it is no known cure for Alzheimer's disease and treatment protocols for Alzheimer's disease depend on the stage of the disease.

The amount of direction present and the presence or absence of working examples

The only direction or guidance present in the instant specification is minimal. There are no working examples present for the treatment of the numerous of diseases and disorders embraced by the claims.

Test assays and procedure are provided in the specification at pages 57-59 for Aminopeptidase A Inhibition Assay. Receptor activity is generally unpredictable and the data provided is insufficient for one of ordinary skill in the art in order to extrapolate to the other compounds of the claims. It is inconceivable as to how the claimed compounds can treat the extremely difficult diseases embraced by the instant claims.

Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved." See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

The breadth of the claims

The breadth of the claims is drawn to a method of treating arterial hypertension and directly and indirectly related diseases, which comprises administering to a patient in need thereof an efficient amount of a compound of formula 1 according to claim 1; a method for treating a disease selected from the group consisting of primary or secondary arterial hypertension, an ictus, myocardial ischemia, cardiac insufficiency and renal insufficiency, myocardial infarction, a peripheral vascular disease, diabetic proteinuria, syndrome X, glaucoma, neurodegenerative diseases and memory disorders, which comprises administering to a patient in need thereof an efficient amount of a compound of formula (1) according to claim 1; or a method of treating ischemic and tumoral pathologies in which aminopeptidase A is involved, which comprises adminstering to a patient in need thereof an efficient amount of a compound of formula (1) according to claim 1.

The quantity of experimentation needed

The quantity of experimentation needed is undue experimentation. One of skill in the art would need to determine what diseases out of all conditions such as neurodegenerative diseases, memory disorders, tumoral pathologies, etc. would be benefited by the inhibition of aminopeptidase A would furthermore then have to determine which of the claimed compounds in the instant invention would provide treatment of the diseases.

The level of the skill in the art

The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by *in vitro* or *in vivo* screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

The specification fails to provide sufficient support of the broad use of the claimed compounds of the invention in a method of treating the numerous diseases and disorders embraced by the claims. As a result necessitating one of skill to perform an exhaustive search for which diseases can be treated by what compounds of the invention in order to practice the claimed invention.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which diseases can be treated by the compound encompassed in the instant claims, with no assurance of success.

This rejection can be overcome, for example, by deleting the method claims.

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 10-12 and 15-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the genus terms "directly and indirectly related diseases" related to arterial hypertension, "an ictus", "a peripheral vascular disease", "neurodegenerative diseases", "memory disorders" and "ischemic and tumoral pathologies" present in the method claims 10-12. The above terms embrace numerous diseases and disorders but Applicants' have failed to define what diseases are included or excluded by the terms. The above terms are not defined in the claims so as to know the metes and bounds of the claims. Therefore, the claims are indefinite.

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 9 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim contains the limitation "selectively inhibiting aminopeptidase A". However, the specification only provides inhibition data for aminopeptidase A. It is well known in the art that the term "selectively" when dealing with inhibition data is used when more than one receptor is tested for inhibitory activity by specific compounds and the compound binds to a receptor preferably over another receptor. Usually there is comparing data between the receptors that were tested in the inhibition assay. According to Applicants' specification, only one enzyme was tested and it is not disclosed that enzymes or receptors were tested.

III. *Objections*

Claim Objections

Claims 6, 14, 16, 18 and 20 are objected to because of the following informalities: the compound 4(s), 4'(S),3(S), 3'(S)-4'-dithiobis-(3,3'-amino-6,6'-phenyl-1,1'hexanesulfonic) acid has too many numbers present.

IV. *Conclusion*

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shawquia Young whose telephone number is 571-272-9043. The examiner can normally be reached on 6:30 AM-3:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on 571-272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

KAMAL A. SAEED, PH.D.
PRIMARY EXAMINER

Shawquia Young
Patent Examiner
Art Unit 1626, Group 1620
Technology Center 1600

Kamal Saeed
Primary Patent Examiner
Art Unit 1626, Group 1620
Technology Center 1600